Utility of Liquid-Based Cytology for Cervical Carcinoma Screening

Results of a Population-Based Study Conducted in a Region of Costa Rica with a High Incidence of Cervical Carcinoma

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BACKGROUND. In a study using a split-sample design, liquid-based cytology (ThinPrep® Processor, Cytyc Corporation, Boxborough, MA) was compared with the conventional Papanicolaou (Pap) smear in Guanacaste, Costa Rica. The study provides the first population-based comparison of the ThinPrep® screening technology and includes "gold standard" measures of diagnostic accuracy.

METHODS. The population-based study was performed among over 8000 women residing in a Costa Rican province with a high incidence of cervical carcinoma. Conventional smears were prepared and diagnosed in Costa Rica, while the residual material on the sampling device was collected into a liquid preservative and shipped to the U.S., where ThinPrep® cytologic slides were prepared and diagnosed. Cytologic diagnoses based on the two techniques, categorized according to the Bethesda System, were compared with a "gold standard" final case diagnosis for each patient, also based on Bethesda terminology, that reflected an integrated interpretation of all available data, including cytology, histology, and cervicography. Results were also compared with the results of HPV DNA detection (Hybrid Capture, Digene Corporation, Silver Spring, MD).

RESULTS. ASCUS was the threshold for colposcopy referral. There were significantly more women referred according to this threshold with the ThinPrep® slide (12.7%) than with the conventional smear (6.7%, $P < 0.001$). Compared with the final case diagnosis, referral by ThinPrep® slides detected 92.9% of cases with high grade squamous intraepithelial lesions (HSIL) and 100% of carcinoma cases. Smears detected 77.8% of HSIL and 90.9% of carcinomas. Thus, ThinPrep® cytology was significantly more sensitive in the detection of HSIL and cancer (McNemar test, $P < 0.001$). Adjudication of cases in which the ThinPrep® and smear diagnoses disagreed, using the final case diagnoses and the HPV DNA test results as reference standards, suggested that the ThinPrep® method was detecting additional true SIL as opposed to false-positives.

CONCLUSIONS. In a population-based study of high risk women, ThinPrep® cytology demonstrated significantly increased sensitivity for detecting HSIL and carcinoma, with a concurrent significant increase in colposcopy referrals. ***Cancer (Cancer Cytopathol)* 1999;87:48–55.** © *1999 American Cancer Society.*

KEYWORDS: cervical carcinoma, screening, cytology, diagnosis.

Papanicolaou (Pap) smear screening is widely recognized as an effective method for preventing cervical carcinoma. Nonetheless, inaccurate and equivocal Pap smear diagnoses related to sampling errors and suboptimal specimen preparations are a serious concern. Recently a new approach to cervical cytology, in which cells collected in liquid preservative are used to prepare ThinPrep® slides (Cytyc Corporation, Boxborough, MA), has been developed in an effort to produce more representative cytologic preparations with fewer artifacts.

In the Cytyc ThinPrep® system, cervical specimens collected with conventional sampling devices are placed directly into vials containing 20 mL of liquid preservative (PreservCyt) rather than being prepared as smears. The vials are transported at an ambient temperature to the cytology laboratory for preparation as liquid-based cytologic slides that are suitable for Papanicolaou staining and cytologic screening. In several trials in which smears and ThinPrep® slides were prepared from split samples, the detection of squamous intraepithelial lesions (SIL) with ThinPrep® slides equaled or exceeded that with smears.[1–6] However, few studies have compared the results of liquid-based cytology with a "gold standard" measure of diagnostic accuracy, and none of the trials reported to date have been population-based.

In this report, the performance of ThinPrep® cytology in a National Cancer Institute–sponsored, population-based study of 10,049 women residing in a Costa Rican province with a traditionally high incidence of cervical carcinoma is assessed. Patients in this study were screened intensively using multiple techniques and then examined with colposcopy and histologic studies if any screening results were abnormal. The "gold standard" diagnosis for each patient reflects the integrated interpretation of all available data. Therefore, this study provides a unique opportunity to assess the utility of various screening techniques in a population-based study of high risk women.

MATERIALS AND METHODS

Case Selection

The subjects were voluntary participants in a National Cancer Institute–sponsored cervical carcinoma screening study conducted in Guanacaste, Costa Rica, a province with a stable standardized cervical carcinoma incidence exceeding 30/100,000 per year. As described in detail elsewhere, 10,049 randomly ascertained subjects were enrolled, representing 15–20% of the women living in Guanacaste.[7] Signed informed consent included a discussion of risks and benefits of participation and the possibility of being called back for new appointments. The current analysis excludes 874 virgins and pregnant women for whom enrollment examinations were deferred and 245 women for whom ThinPrep® or smear results were not prepared or not available. Also excluded were 16 women whose conventional smear and ThinPrep® slide were both unsatisfactory, 225 women whose ThinPrep® slide was unsatisfactory, and 53 women whose smear was unsatisfactory. This left 8636 cases with full data suitable for final analysis.

Specimens

Exfoliative cervical samples obtained with the Cervex brush (Unimar, Wilton, CT) were taken from consenting subjects and prepared as conventional cervical smears that were spray-fixed with Pap Perfect (Medscand, Hollywood, FL). After the slides were smeared with both sides of the brush, the residual cells remaining on the sampler were rinsed into vials containing 20 mL of preservative (PreservCyt). An additional sample was obtained with a dacron swab and placed in specimen transport medium (STM) for future human papillomavirus (HPV) DNA testing using the first generation Hybrid Capture tube test (Digene Corp., Silver Spring, MD). The cancer-associated HPV types 16, 18, 31, 33, 35, 45, 51, 52, and 56 are included in this test.[8] Finally, the cervix was rinsed with 5% acetic acid, and 2 cervigrams (high resolution photographs of the cervix) were obtained.

Pathology Review

Each subject was screened with three cytologic methods, performed independently in different laboratories and reported without knowledge of the other results or HPV test data. The cervical smears were stained with a modified Papanicolaou technique in Costa Rica and then screened and reported according to the Bethesda System (TBS). Prior to the study, the members of the cytology laboratory were trained in the use of TBS. The cytology laboratory also received technical consultation regarding the performance of the Papanicolaou stain before and at one point during enrollment.

After conventional microscopic screening and diagnosis in Costa Rica, the smears (with screening marks removed) were shipped to the U.S. for study with a semiautomated cervical cytology screening system (PapNet System, Neuromedical Systems Inc., Suffern, NY). The results of this computer-assisted screening were available for the majority of smears and were included as one of several criteria for determining the final case diagnoses. Results of the computer screening are reported elsewhere.[9]

The cellular samples that were fixed in PreservCyt

were transported to the U.S. for preparation as ThinPrep® slides. Briefly, ThinPrep® slides were prepared by placing a PreservCyt vial and a microscopic slide on the ThinPrep® processor, which mixes the sample and draws cells onto a membrane filter by suction. When the filter has collected sufficient cells to produce a slide, the suction is released and the cells are transferred to a 20-mm circular area on a glass slide under slight positive pressure. The slide is then immersed in 95% ethanol and stained by a modified Papanicolaou method. All of the ThinPrep® slides were screened in the U.S. and then reviewed and diagnosed by a single pathologist (M.H.) according to TBS. For this study, the Beta model of the ThinPrep® processor was used (the current model, the ThinPrep® 2000, is the only model approved by the Food and Drug administration for the Pap test; it places more cells on the slide and allows a wider range of specimen variability).

The cervigrams (National Testing Laboratories, Fenton, MO) were processed in the U.S. and interpreted by expert reviewers (principally M.G.) who were masked to other screening test results. Cervigrams were reported as normal, atypical, P0 (probably normal but cannot rule out a significant lesion), or Pl–P3 (increasing grades of abnormality). Positive cervigrams were defined as P0, P1, P2, or P3 for purposes of referral to colposcopy. The cervigram interpretation was used in the determination of the final case diagnosis, but only as part of the definition of low grade squamous intraepithelial lesions (LSIL) and equivocal categories. The cervigram results from this study have been reported elsewhere.[10]

Colposcopy Referral and Management

To summarize, the criteria for colposcopy referral included a physical examination suspicious for cancer or another gynecologic emergency (which occurred uncommonly); a cytologic diagnosis of atypical squamous or glandular cells of undetermined significance (ASCUS), SIL, or carcinoma by any of the three methods (smear, ThinPrep®, or PapNet testing); or a positive cervigram (P0–P3). Women with a biopsy-confirmed high grade squamous intraepithelial lesion (HSIL) were treated with large loop excision of the transformation zone. Women with a single cytologic diagnosis of HSIL confirmed on cytologic review were also treated if a lesion was identified colposcopically and there were no contraindications to treatment. Women with a discrepancy between cytology and colposcopy were treated if recommended after an independent review. The remaining women were referred through the Social Security System for follow-up. Biopsy specimens were diagnosed initially in Costa Rica for clinical purposes and then reviewed in the U.S. Final treatment decisions were rendered by the responsible physicians in Costa Rica. The virtual 100% sensitivity of the multitest screening protocol was confirmed by a finding of no SIL in a random sample of 150 women in the cohort referred for colposcopy despite completely negative screening test results (to serve as negative controls).

HPV DNA Testing

HPV DNA testing methods for this study are described in detail elsewhere.[11] In brief, HPV DNA testing was performed at Digene Corporation. An aliquot of specimen was taken from the thawed STM tube. Specimens in STM were denatured with sodium hydroxide and were reacted with RNA probes directed against the cocktail of HPV types. In HPV containing samples, hybrids composed of HPV DNA and the corresponding full-length RNA probe were captured by immobilized antibody against RNA:DNA hybrids. Positive reactions were detected by adding an alkaline phosphatase–tagged antibody that also recognized DNA:RNA hybrids and measuring the light emission resulting from the dephosphorylation of a dioxetane substrate with a luminometer. Positive reactions were defined as samples with light emission exceeding the mean of three positive controls containing HPV type 16 at 10 pg/mL of reaction mixture. HPV testing results were not used in clinical decision-making or in determining the final case diagnoses.

Analysis

Final case diagnoses reflected the interpretation of all screening tests and histopathologic specimens. Final case diagnoses of negative were conferred on women with negative screening tests, women referred to colposcopy for ASCUS cytology in whom a lesion was excluded, and occasionally women downgraded to negative by final review despite initially positive cytologic findings. Diagnoses of LSIL included biopsy-confirmed lesions and cases confirmed on cytologic review by two or more methods. Histologic confirmation was obtained in 93% of HSILs and 100% of invasive carcinomas. Final case diagnoses of equivocal were conferred on women with various combinations of results, including a single cytologic diagnosis of LSIL by any method, an isolated positive cervigram, or equivocal results based on the review of all available data.

ThinPrep® diagnoses were compared with the smear diagnoses rendered in Costa Rica, final case diagnoses, and the detection of carcinogenic types of HPV DNA using the Hybrid Capture tube test. Because the threshold for colposcopy referral in this study was a cytologic diagnosis of ASCUS, cytologic screening

TABLE 1
ThinPrep® versus Conventional Smear Diagnoses

	Conventional smear					
ThinPrep® slide	Negative	ASCUS	LSIL	HSIL	Carcinoma	Total
Negative	7264	122	137	18	0	7541
ASCUS	569	20	43	15	3	650
LSIL	177	12	64	41	1	295
HSIL	46	5	17	56	15	139
Carcinoma	1	0	1	3	6	11
Total	8057	159	262	133	25	8636

ASCUS: atypical squamous or glandular cells of undetermined significance; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

TABLE 2
ThinPrep® versus Final Case Diagnoses

	Final case diagnosis					
ThinPrep® slide	Negative	Equivocal	LSIL	HSIL	Carcinoma	Total
Negative	7087	415	30	9	0	7541
ASCUS	520	103	14	10	3	650
LSIL	1	160	111	23	0	295
HSIL	9	17	31	76	6	139
Carcinoma	0	1	0	8	2	11
Total	7617	696	186	126	11	8636

ASCUS: atypical squamous or glandular cells of undetermined significance; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

results were stratified into negative (normal or reactive) and positive (ASCUS, LSIL, HSIL, and carcinoma) for analytic purposes. The discrepant results between ThinPrep® and conventional cytology were adjudicated by comparison with the final case diagnoses and the detection of carcinogenic types of HPV DNA. Statistical analyses were performed using standard contingency table methods.

RESULTS

ThinPrep® Slides Compared with Conventional Smears

ThinPrep® and conventional smear diagnoses (Table 1) agreed in 7410 (85.8%) of the 8636 cases and were within 1 category in 8232 cases (95.3%). Of women referred for colposcopy because of a cytologic diagnosis of ASCUS or worse, 1095 (12.7%) were referred because of an abnormal ThinPrep® diagnosis and 579 (6.7%) were referred because of an abnormal smear result. This increase in positive diagnoses by the ThinPrep® method was statistically significant ($P < 0.001$). The vast majority of the agreement was accounted for by concurrence on slides that were negative. Among smears classified as abnormal by at least one method, agreement regarding abnormality (and the level of abnormality) was poor. There were considerably more ThinPrep® slides than smears diagnosed as ASCUS. For 224 women (2.6% of the total), the ThinPrep® slide was diagnosed as SIL or carcinoma and the smear was reported to be negative, whereas for 155 patients (1.8%) the smears were diagnosed as SIL and the ThinPrep® preparations were reported to be negative.

ThinPrep® Diagnoses Compared with Final Case Diagnoses

ThinPrep® diagnoses agreed with final case diagnoses in 7379 (85.4%) of the 8636 subjects (considering ThinPrep® diagnoses of ASCUS and final diagnoses of equivocal as equivalent, Table 2). Based on colposcopy referral of all women with cytologic diagnoses of ASCUS or worse, ThinPrep® preparations detected l56 (83.9%) of 186 women with a final diagnosis of LSIL, 117 (92.9%) of 126 subjects with a final diagnosis of HSIL, and 11 (100.0%) of 11 with a final diagnosis of carcinoma. Conversely, in 520 women with ASCUS ThinPrep® results and 10 with SIL, the final case diagnosis was judged to be negative.

TABLE 3
Conventional Smear versus Final Case Diagnoses

	Final case diagnosis					
Conventional smear	Negative	Equivocal	LSIL	HSIL	Carcinoma	Total
Negative	7489	467	72	28	1	8057
ASCUS	111	36	7	4	1	159
LSIL	0	172	75	15	0	262
HSIL	17	18	32	63	3	133
Carcinoma	0	3	0	16	6	25
Total	7617	696	186	126	11	8636

ASCUS: atypical squamous or glandular cells of undetermined significance; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

TABLE 4
ThinPrep® Slide versus Conventional Smear for Cases with Final Diagnoses of HSIL

	Conventional smear					
ThinPrep® slide	Negative	ASCUS	LSIL	HSIL	Carcinoma	Total
Negative	8	0	1	0	0	9
ASCUS	2	1	1	4	2	10
LSIL	2	0	4	16	1	23
HSIL	15	3	8	41	9	76
Carcinoma	1	0	1	2	4	8
Total	28	4	15	63	16	126

ASCUS: atypical squamous or glandular cells of undetermined significance; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

Conventional Pap Smears Compared with Final Case Diagnoses

Smear diagnoses agreed with final case diagnoses in 7669 (88.8%) of 8636 subjects (considering smear diagnoses of ASCUS and final diagnoses of equivocal as equivalent, Table 3). Based on colposcopy referral of all women with cytologic diagnoses of ASCUS or worse, smears identified 114 (61.3%) of 186 women with a final diagnosis of LSIL, 98 (77.8%) of 126 subjects with a final diagnosis of HSIL, and 10 (90.9%) of 11 with a final diagnosis of carcinoma. For 111 women with ASCUS smear results and 17 with SIL, the final case diagnosis was negative.

Final Case Diagnoses for Women in Whom HSIL Was Diagnosed by Either ThinPrep® or Smear but the Other Method Was Negative

In Table 1, there were 46 women in whom ThinPrep® cytology revealed HSIL and the smear was negative and 18 women in whom HSIL was detected with conventional cytology alone. The 46 HSILs diagnosed with ThinPrep® slides alone included 38 cases subclassified on ThinPrep® as cervical intrathelial neoplasia (CIN) 2 and 8 subclassified as CIN 3. The final case diagnoses for these patients were negative for 7 (15.2%); equivocal for 10 (21.7%); LSIL for 14 (30.4%); and HSIL for 15 (32.6%). The smear diagnosis for 16 of 18 HSILs diagnosed with smears only was CIN 2; the remaining 2 were CIN 3. The final case diagnoses for these patients were negative in 11 (61.1%), equivocal in 5 (27.8%), and LSIL in 2 (11.1%). The discrepant HSILs diagnosed by ThinPrep® slides were more numerous than those diagnosed only with smears, and the ThinPrep® discrepant HSILs were more likely to have SIL confirmed on final diagnosis (29 of 46 vs. 2 of 18, $P < 0.001$).

ThinPrep® and Smear Diagnoses for Women with a Final Diagnosis of HSIL

Conversely, a comparison of ThinPrep® with smear cytology for those cases with a final diagnosis of HSIL is shown in Table 4. Using ASCUS as the colposcopy threshold, 117 (92.9%) of the 126 women with a final diagnosis of HSIL were detected with ThinPrep®, as compared with 98 (77.8%) with smears. This increase in sensitivity by the ThinPrep® method was statistically significant (McNemar test, $P < 0.001$), and was maintained when detection of carcinomas was added to the HSILs. Viewed another way, compared with smears, the ThinPrep® method achieved a reduction

TABLE 5
HPV DNA Detection, According to ThinPrep® and Smear Diagnoses

Diagnosis	ThinPrep® slides	HPV detection	Smears	HPV detection
Negative	7535	368 (4.9%)	8050	529 (6.6%)
ASCUS	649	87 (13.4%)	159	22 (13.8%)
LSIL	295	184 (62.4%)	261	89 (34.1%)
HSIL	138	102 (73.9%)	133	93 (69.9%)
Carcinoma	11	9 (81.8%)	25	17 (68.0%)

HPV: human papillomavirus; ASCUS: atypical squamous or glandular cells of undetermined significance; LSIL: low grade squamous intraepithelial lesion; HSIL: high grade squamous intraepithelial lesion.

in the false-negative rate for HSIL/carcinoma of about two-thirds. Of the missed cases, eight were missed on both the ThinPrep® slides and the smears, indicating a possible cervical sampling error.

HPV Test Results Compared with ThinPrep® and Conventional Smear Diagnoses

HPV DNA was detected in 62.4% of women with ThinPrep® diagnoses of LSIL, 73.9% with HSIL, and 81.8% with carcinoma (Table 5). HPV was detected in 34.1% of women with LSIL diagnosed based on smears, 69.9% with HSIL, and 68.0% with carcinoma. HPV detection tended to be higher for ThinPrep® slides among women with SIL, particularly LSIL.

Detection of Oncogenic HPV Types in Cases with Discordant ThinPrep® and Smear Results

HPV data were available for 1069 pairs of discordant (positive/negative screening) results in which both the smear and ThinPrep® slide were satisfactory specimens. An oncogenic type of HPV DNA was detected in 54 (6.8%) of 792 women with positive ThinPrep® cytology (≥ASCUS) and negative conventional smears as compared with 4 (1.4%) of 277 women with negative ThinPrep® slides and positive smears (≥ASCUS). The higher prevalence of oncogenic HPV in the ThinPrep® positive discordant cases was statistically significant ($P < 0.001$).

DISCUSSION

The results of ThinPrep® cytology agreed with the final case diagnoses in 85.4% of cases in this study, comparable to the 88.8% agreement of smear cytology. However, analysis of abnormal final diagnoses showed important differences in the two methods. Using ASCUS as the threshold for colposcopy referral, ThinPrep® cytology would have resulted in the referral of 12.7% of women as well as the detection of 92.9% of patients with a final diagnosis of HSIL and 100% of those with carcinoma. In comparison, conventional cytology would have resulted in the referral of 6.7% of women, detecting 77.8% with HSIL and 90.9% with carcinoma. Thus, the sensitivity of ThinPrep® cytology was higher than conventional cytology in this study, but the proportion of women referred for colposcopy was greater. The performance achieved with both the conventional smear and the ThinPrep® was superior to the 50% (95% confidence interval, 49–67%) sensitivity and 69%(95% confidence interval, 62–77%) specificity reported in the meta-analysis by Fahey et al.[12]

Based on the reference standards that were employed, many of the additional referrals based on the ThinPrep® method represented SIL. Based on the final case diagnoses, 29 (63%) of 46 women with ThinPrep® preparations diagnosed as HSIL paired with negative smears were considered to have SIL. In contrast, a final diagnosis of SIL was established in only 2 (11%) of 18 women with smears diagnosed as HSIL and negative ThinPrep® preparations. Similarly, HPV detection in women with abnormal ThinPrep® slides and negative smears was higher than that in women with abnormal smears and negative ThinPrep® slides. This probably, in part, reflects different criteria for the category of LSIL, but the comparison still reflects well on the specificity of the ThinPrep® method.

An important function of cervical cytology is to stratify patients according to cancer risk. Given that nearly all carcinoma is related to HPV, the rate of detection of oncogenic types of HPV should be higher among women with SIL than among women with ASCUS smears and lowest among women with negative cytology. This correlation has been demonstrated in a previous study in which the cytologic diagnoses of five pathologists using TBS was compared with HPV DNA detection.[13] In the current study, HPV was detected in 4.9% of women with negative ThinPrep® cytology, 13.4% with ASCUS, 66.1% with SIL, and 81.8% with carcinoma. These results demonstrate that the severity of ThinPrep® cytologic diagnoses is strongly associated with HPV detection. The association between smear diagnoses and HPV detection were similar, but smear diagnoses of LSIL were associated with nearly a 50% lower level of HPV detection, suggesting that many reactive smears were misclassified as LSIL. Results from recent U.S. studies using HPV testing methods similar to the one used in this study have consistently detected HPV DNA in approximately 60–80%

of women with LSIL diagnosed by different pathologists.[13] Thus, in the U.S., cytologic diagnoses of LSIL are nearly synonymous with HPV infection. However, in this study this suggests that different diagnostic criteria for LSIL may have been applied.

Although not part of the study design, a referral threshold of LSIL could be theoretically applied to the data. This would result in similar rates of referral to colposcopy: 5.2% for the ThinPrep® method and 4.9% for the smear. Of the cases with a final diagnosis of HSIL or carcinoma, the ThinPrep® method would pick up significantly more cases (115) than the smear method (103; $P < 0.05$). It is noteworthy that for the three cases with a final diagnosis of carcinoma that were diagnosed as ASCUS by the ThinPrep® method, two of the ThinPrep® slides were signed out "AGUS can't rule out AIS or malignancy," and one was signed out "ASCUS can't rule out HSIL." It is possible that a refined referral threshold, including ASCUS smears, where the differential is with HSIL, may preserve most of the sensitivity while reducing the number of referrals. This needs to be further investigated by both the ThinPrep® method and the conventional smear.

The "gold standard" final case diagnoses in this study reflect the results of an intensive screening effort coupled with comprehensive workup, including colposcopy and histologic studies. Based on the absence of significant pathology in a random sample of 150 subjects in this study with negative screening results who were examined colposcopically, we believe that nearly all of the disease in the population under study was detected. Therefore, we think that the detection of SIL using ThinPrep® cytology in this study represents an accurate estimate of the sensitivity of the method. Previous studies demonstrating close to 90% diagnostic agreement between smears and ThinPrep® slides prepared from split samples demonstrated the comparability of these two methods but did not permit the sensitivity determinations that have been presented in this report.

Although the intense screening effort presented in this study permitted the assignment of a "gold standard" diagnosis for most subjects, extrapolation of our results to other populations has certain limitations. First, the cervical carcinoma incidence in the population studied is approximately five times that in most U.S. populations. Therefore, the predictive values of cytologic techniques in well-screened groups may be different. Second, direct comparisons between smear and ThinPrep® diagnoses is difficult because the slides were interpreted in different laboratories. This can be seen in the ASCUS:LSIL ratios and in the unsatisfactory rates in the two laboratories, suggesting different adherence to the criteria of TBS. Although the ASCUS:LSIL ratio with the ThinPrep® was 2.2:1 and the ratio with the conventional smear was 0.6:1, the respective LSIL:HSIL ratios were virtually identical (2.0:1 and 2.1:1, respectively). ThinPrep® ASCUS:LSIL ratios and the unsatisfactory rate were both consistent with those from most U.S. laboratories. Third, it is noteworthy that the quality of the Papanicolaou stain that was applied to the smears was not optimal. Similarly, the ThinPrep® processor that was used in this study has subsequently been updated and improved. Use of the new ThinPrep® 2000 model, which presents 40% more cells, with Costa Rica follow-up cases has resulted in a decrease in the number of unsatisfactory slides. Finally, the ThinPrep® slides were prepared from rinses of the samplers after the conventional smear was made rather than from the entire specimen, perhaps in some cases resulting in a reduction in the number of diagnostic cells that reached the vial. Despite these limitations, our data suggest that the performance of ThinPrep® cytology was more sensitive in detecting HSIL than smears, albeit with a substantial increase in referral of patients for colposcopy.

In summary, this study extends previous work suggesting that the ThinPrep® method is at least as good as conventional cytology in detecting SIL and carcinoma. In this population-based study, the clinical effectiveness, particularly regarding detection of HSIL, is demonstrated. The clinical utility of the ThinPrep® method, and its cost-effectiveness in particular, are now being evaluated as more experience is gained with the technique in clinical practice.

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